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EXAMINER
SACKEY, EBENEZER O

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,386	SHINITZKY, MEIR	
	Examiner	Art Unit	
	EBENEZER SACKEY	1626	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5, 11-23, 25-27, 31, 32, 36-37 and 44-46* is/are rejected.

7)☒ Claim(s) *1,5,9, 11,12,14-22 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-37 and 44-46 are pending.

This is a response to applicants' amendment filed on 06/25/03. Applicant has cancelled claims 38-43, drawn to non-statutory "use" claims. New claims 44-46 have been added. Applicant's attorney correctly stated that the current application has only one inventor. The correction is noted.

In view of applicant's argument filed on 06/25/03, the restriction requirement instituted in the last office has been withdrawn.

Response to Restriction

Applicant's election with traverse of Group I, species of claim 9 i.e., phenyl 1,3-cyclicglycerophosphate in Paper No. 3 is acknowledged. The traversal is on the ground(s) that phenyl 1, 2-cyclicglycerophosphate (claim 6) is structurally similar to be included with the elected species of claim 9. This is found persuasive and as previously stated, the restriction requirement has been withdrawn. Therefore, applicants' argument is moot with regards to the restriction requirement. New grounds of rejections appear below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 26, 27, 36 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human breast cancer cells and T-leukemia cell lines, does not reasonably provide enablement for all malignant diseases and disorders and diseases which can be treated by phosphorylation of intracellular proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Level of ordinary skill in the art.

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See below:

1) Nature of the invention.

The claims are drawn to pharmaceutical compositions containing compounds of formulae (I) and (II) for the treatment of malignant diseases and disorders and diseases and disorders, which can be treated by phosphorylation of intracellular proteins.

2) State of the prior art.

The specification does not indicate which specific diseases are being treated. Applicant cites a reference on pages 29 and 30 of the specification that pertains to the effects of cyclic phosphates on differentiation of human breast cancer cells and T-leukemia cell lines without any further disclosure of other specific diseases.

3) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Malignant diseases and disorders and phosphorylation of intracellular proteins encompasses a vast number of diseases and disorders such as disclosed in U.S.Patent number 6,504,014 that a class of peptide prodrugs which contain cleavage sites specifically cleaved by prostate specific antigen (PSA) are useful for inhibiting the non-specific toxicity of a variety of therapeutic drugs. Upon cleavage of the prodrug by (PSA) the therapeutic drugs are activated and exert their toxicity. Applicant's specification does not enable the public at large to treat such numerous amounts of diseases and disorders encompassed by the instant treatment. Additionally, the intended use of the composition is given no patentable weight.

4) Level of predictability in the art.

The art pertaining to the treatment of malignant diseases and disorders and phosphorylation of intracellular proteins remains highly unpredictable. Treatment of malignant diseases or phosphorylation of intracellular proteins require various experimental procedures and without guidance that is applicable to all malignancies or phosphorylations, there would be little predictability in performing the claimed invention.

5) Amount of direction and guidance provided by the inventor.

Malignancies or phosphorylations encompasses a vast number of treatments. Applicant's limited guidance does not enable the public to treat such numerous amount of diseases encompassed by the instant invention. It is not believable in view of the contemporary knowledge of the art that one compound or composition would have the capacity to treat an extra ordinary amount of malignancies which require different pathways and mechanisms. There is no enablement for all malignancies or disorders. In addition, it is noted that the specification does not define or provide disclosure for specific malignancies.

6) Existence of working examples.

As discussed above, malignancies and phosphorylation of intracellular proteins encompasses a vast number of diseases which may have different types mechanisms and pathways. For example, could cervical, pancreatic or lung malignancies be embraced by the instant claims. Applicant's limited working examples do not enable the public to prepare such numerous diseases encompassed by the instant invention. Applicant claims a plethora of diseases which is not supported by the specification.

7) Breadth of claims.

The claims are extremely broad due to the vast number of possible malignancies and disorders that can be treated from the instant invention.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification does not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with these claims. In particular, the specification failed to enable the skilled artisan to practice the invention without undue experimentation. The skilled artisan would have numerous amounts of modifications to perform in order to treat malignancies as instantly claimed.

Based on the unpredictable nature of the invention and state of the prior art and the extreme breadth of the claims, one skilled in the art could not perform the claimed invention without undue experimentation; see In re Armbruster 185 USPQ 152 CCPA 1975.

It is noted that there is a typographical error in spelling "phenyl" in claim 1. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 25, 31, 32, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following phrases are not supported in the specification: In claims 17, 31 and 32 "hormone-like signaling" page 6, line 2 and page 10, line 2-3 respectively; claim 25 "disorders" page 9, line 2; claim 37 "abnormal conditions" page 11, line 2. The specification fails to adequately teach how to use the invention properly by failing to provide an enabling disclosure regarding the above phrases. Because of the high level

of unpredictability associated with chemical or biological systems, a greater amount of evidentiary support is needed in order to fully satisfy the requirement of 35 U.S.C. 112, first paragraph, that applicants provide sufficient guidance as regards "how to use" the invention. For example what is encompassed or contemplated by "hormone-like signaling"? The specification only supports insulin, human growth hormone and epidermal growth factor? Clearly, a great deal of experimentation would be required to ascertain what is encompassed by the phrase. It is also not clear what is contemplated by disorders. Disorders appear in various ways and forms. For example headache, rubella, mumps etc. Currently the diseases or disorders with adequate support are leukemia and breast cancer. Because of the various pathways and mechanisms associated with other disorders such as for example pancreatic cancer, greater amounts of evidentiary support would be required for the instant claims. These expressions consist of for example any possible disorder or abnormal conditions known. The specification has shown that the testing protocol used on pages 22 may be accepted in the art as being predictive of the utility alleged. Merely identifying substances as objects for further use-testing (speculative utility) is insufficient to provide an enabling disclosure. See Brenner V. Manson, 148 USPQ 689 or In re Kirk, 153 USPQ 48. Additionally, "hormone-like, abnormal conditions, disorders etc" are generic. As defined, the claims embrace a variety of conditions and/or disorders, which are broader than the enabling disclosure.

Applicants need to point out in the specification where there is support for the above phrases. A mere statement does not provide enabling support for such a utility.

In the instant application, the specification is not enabling for the broad class of disorders and conditions etc., encompassed by the invention because the limited test data does not support all of the above expressions. In view of the unpredictability of

chemical systems, and the fact that specific disorders and conditions have not been shown to be effective for the invention, a conclusion of this activity cannot be reached without data for the entire scope of the invention.

In addition, the gap between limited laboratory activity and industrial utility is large enough to warrant thorough and compelling data.

Of course, the inclusion of some inoperative embodiments in a generic claim is not enough in itself to render the claim unpatentable. However, when the number of inoperative embodiments becomes significant, or when the likelihood is high that a significant number of the embodiments are inoperative, one of ordinary skill must resort to undue experimentation to practice the claimed invention, and at this point the generic may properly be found to be unpatentable. See Atlas Powder Co. V. E.I. Dupont de Nemours, 750 F .2d 1569, 1576 (Fed. Cir. 1984).

"In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty in their performance characteristics predicted by resort to know scientific law. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of factors involved." Amgen, Inc. V. Chugai Pharmaceutical Co. Lts., 13 USPQ .2d 1737, 1775 (1980), citing In re Fisher, 527 F .2d 833, 839 (CCPA 1970). The Amgen decision, Id. At 1776, went on to point out that, while 50 to 80 analogs had been tested in vitro and exhibited activity varying over several orders of magnitude, this was not sufficient to conclude that the same analogs would have comparable biological activity. The case of non-enablement was therefore found to be even stronger against the remaining analogs encompassed by the implicated claim, for which in vitro data had been furnished. After

extensive testimony, the claim was held invalid for the failure to satisfy the enablement requirement of sec. 112.

The present rejection is believed to be consistent with the aforementioned decisions, as well as the decision in In re Marzocchi, 169 USPQ 367, 369 (1971) in which the court stated that:

"As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proof indicating that the teaching contained in the specification is truly enabling."

By suggesting that specific disorders or conditions may be required to show that the instantly claimed invention satisfies that enablement requirement, the Examiner does not wish to determine the lack of inhibitory activity of the claimed method of using the composition, but rather to determine if specific disorders or conditions benefit have been attained.

The specification is devoid of disclosure, which would direct the skilled artisan to all disorders or conditions embraced by the above claims. It is suggested that specific conditions or disorders be disclosed. Such would appear to obviate the rejection. However, applicants should note that the insertion of disorders or conditions etc., into the specification or claims could raise the issue of new matter.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 11-23, 44 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Ayres et al. (The Organic Chemistry of Phosphorus, Part V.) "Ester interchange Reaction between Triphenyl Phosphite and Glycols", 1957, pages 1109-1114 or Shinitzky et al., "Formation of 1,3-cyclic Glycerophosphate by the Action of Phospholipase C on Phosphatidylglycerol", Jour. Of Biological Chemistry, 1993, vol. 268, No. 19, pages 14109-14115 or Denney et al., "Preparation and Chemistry of 2,6,7-trioxa-1-phosphabicyclo[2.2.1]heptane", Phosphorus and the Related Group V Elements (1973), 2(5-6), 245-8 or Haimovitz et al., "Neuronal outgrowth and rescue induced by cyclic phosphates in PC12 cells", Life Sciences (2001), 69(23), 2711-2723.
Applicant claims compounds and compositions of formulae (I) and (II). Denney et al., disclose compounds and compositions which are identical to the instantly claimed compounds when X is H; Y is CH(OH) and R is methyl. Haimovitz et al., disclose compounds and compositions which are identical to the instantly claimed compounds when X is H; Y is CH(OH) and R is H. Ayres et al., disclose 1,3-cyclic glycerophosphate compound wherein Y is CH_2, X is H and R is phenyl. See the entire publication especially page 1111, compound VII. See also the entire publication of Shinitzky et al.

Claim Rejections - 35 U.S.C. § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1, 2, 5, 22, 23, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al., (U.S.Patent Number 6,346,594).

Applicant claims compounds of formula (I), a pharmaceutical composition comprising the compounds and methods of using the compound to treat various disease states.

Determination of the scope and content of the prior art (MPEP §2141.01)

Watanabe et al., disclose compounds, which are similar to the instantly claimed compounds. See the entire reference, for example column 23, 2-methoxy-2-oxo—1,3,2-dioxaphospholane i.e. when Y is $(CH_2)_m$ wherein m is 0, X is H and R is methyl.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The instant compounds differ from the reference compounds in the definition of R on the dioxo ring. See for example wherein R is alkyl in each of formulae (I) and (II) which corresponds to CH_3 in the reference.

Finding of prima facie obviousness---rational and motivation (MPEP §2142-2143)

One of ordinary skill in the art at the time of this invention would have found the instant compounds obvious over the references since the references generically embrace the instant compounds. See *In re Lemin,* 332 F.2d 839, 141 USPQ 814(1964). Additionally, it is well settled that a reference may be relied upon for all that it would have reasonably conveyed to the skilled artisan, *In re Lamberti* 545 F.2d 747, 192 USPQ 278 (1976). Accordingly, one of ordinary skill in the art would thus have been motivated to prepare compounds embraced by the disclosed reference with the expectation of obtaining additional compounds for medical use. Furthermore, the motivation to prepare these compounds is their close structural similarities to the disclosed compounds of the reference. Thus, the skilled artisan would expect the close structural similarities of the compounds to possess similar properties. While homology is considered to be present even if true homology is not present, such does not defeat the prima facie case of obviousness raised by the art. See *In re Druey et al.,* 50 CCPA 1538, 319 F.2d 237, 138 USPQ 39, wherein Judge Worley, delivering the Court's opinion, stated:

"We need not decide here whether the compounds in question are properly labeled homologues. It appears to us from the authorities cited by the solicitor and appellants that the term homologue is used by chemists at times in a broad sense, and at other times in a narrow or strict sense. The name used to designate the relationship between the related compound is not necessarily controlling; it is the closeness of that relationship which is indicative of the obviousness or unobviousness of the new compound".

Moreover, the motivation as to why one of ordinary skill would conceive and use similar compounds was rendered by the Court which stated in *In re Gyurik et al.,* 596 F.2d 1012, 201 USPQ 552 at 557 that:

"In obviousness rejections based in close similarity in chemical structure, the necessary motivation to make a claimed compound, and thus the prima facie case of obviousness rises from the expectation that compounds similar in structure will have similar properties".

The instantly claimed invention would thus have been suggested to one of ordinary skill.

Claims 3-4, 6-10, 24, 28-30, 33-35 are objected to for depending on rejected based claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to E. Sackey whose telephone number is (703) 305-6889. The examiner can normally be reached on Monday-Friday from 7:30 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (703) 308-4537. The fax phone

number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

EOS
September 8, 2003

Joseph K. McKane
Supervisory Patent Examiner
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Technology Center 1